REMARKS/ARGUMENTS

Status of the Claims

Upon entry of the present amendment, claims 1-7, 9, 12-32, 35-40 and 56-58 are pending. Claims 10-11 are canceled without disclaimer or prejudice to renewal.

No new matter is added by the present amendments, and the Examiner is respectfully requested to enter them.

Information Disclosure Statement

The Examiner objected to the IDS filed on June 19, 2006, requesting the correction of the citation of Mills, *et al.*, *Drug Metab Rev* (2002) 34:124, Abstract #248 ("Mills"). In response, Applicants attach an IDS with the correct citation for Mills.

Specification

The Examiner objected to the specification, requesting that the address to ATCC be updated. In response, Applicant have updated the relevant paragraph on pages 6, 16 and 19.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 10 and 11 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants do not agree with the Examiner. However, in the interest of furthering prosecution, Applicants have canceled claims 10 and 11. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 112, first paragraph, enablement

The Examiner has rejected claims 31 and 32 under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. In particular, the Examiner is requesting that Applicants submit a Declaration attesting to cell lines identified in the present application as Fa2N-4 (ATCC # PTA-5566) and Ea1C-35 (ATCC # PTA-5565) have been deposited under the terms of the Budapest Treaty and that all restrictions on the availability to the public of the deposited cell

lines, *i.e.*, Fa2N-4 (ATCC # PTA-5566) and Ea1C-35 (ATCC # PTA-5565), will be irrevocably removed upon issuance of the patent. In response, Applicants submit with this response a Declaration under 35 C.F.R. § 1.808 attesting to this deposit.

Rejections under 35 U.S.C. § 102

XenoTechniques publication

The Examiner has rejected claims 1-7 and 9-32 under 35 U.S.C. § 102(a) as allegedly anticipated by XenoTechniques (2003) 1(1) 1-11. This rejection is respectfully traversed because the cited XenoTechniques publication is not prior art. The present application claims priority to U.S. Provisional Application No. 60/510,509, filed on October 10, 2003. In contrast, the disclosure in the XenoTechniques publication was first published on October 12, 2003. Applicants provide as Exhibit 1 a communication from Maciej Czerwinski of XenoTechniques notifying of the original dissemination of the disclosure in the XenoTechniques publication at the October 12-16, 2003 ISSX Meeting in Providence, Rhode Island.

Regardless, Applicants demonstrate with the accompanying Declaration under 37 C.F.R. § 1.131 the conception and reduction to practice of the claimed immortalized hepatocytes prior to October 27, 2002, well before October 12, 2003.

Accordingly, the XenoTechniques publication is not prior art.

Mills, *et al.*, *Drug Metab Rev* (2002) 34:124, Abstract #248 ("Mills")

The Examiner has rejected claims 1-7 and 9-31 under 35 U.S.C. § 102(a) as allegedly anticipated by Mills. This rejection is respectfully traversed because Mills is not prior art. The Mills abstract was presented October 27-31, 2002 at the Annual ISSX Meeting in Orlando, Florida. Applicants submit with this response a Declaration under 37 C.F.R. § 1.131 attesting to the conception and reduction to practice of the claimed immortalized hepatocytes prior to the October 27, 2002 publication of Mills. Accordingly, Mills is not prior art.

U.S. Patent No. 5,665,589 ("Harris")

The Examiner has rejected claims 1-7, 12-21, 23-25 and 28-30 under 35 U.S.C. § 102(b) as allegedly anticipated by Harris. This rejection is traversed for the reasons set forth below.

As the Examiner appreciates, proper anticipation requires that the cited reference teach each and every element of the rejected claims. M.P.E.P, § 2131.

Here, Harris discloses human liver epithelial cell lines which replicate indefinitely in culture. However, the cells of Harris do not appear to be stable in culture, and there is strong evidence that the cells of Harris do in fact undergo dedifferentiation. Moreover, these cells, designated in Harris as THLE cells, do not have the stable phenotypic characteristics of hepatocytes. This is shown by the following quotation from Harris at column 10, lines 31-66 (references omitted):

> **Early passage THLE-2 and THLE-3 cells formed colonies with mixed ability to secrete albumin. We hypothesize that these cells constitute dedifferentiated hepatocytes that have varying ability to express albumin or arose from liver stern cells differentiated to cells with hepatocyte characteristics. In rats treated with hepatic carcinogens or toxic compounds, oval cells that are much smaller than parenchymal hepatocytes or nodular cells are observed. Oval cells can differentiate to liver parenchymal cells under particular conditions in vivo suggesting that these cells may be stem cells with the potential of being neoplastically transformed to cholangiocellular, as well as hepatocellular carcinomas. Rat oval cells are characterized by the expression of phenotypic markers such as albumin, cytokeratin 18 and 19, γ-GT, α-fetoprotein and glutathione-S-transferase pi, whereas 6-glucose phosphatase activity is only weakly positive. THLE cells have an epithelial morphology; early passage cells secreted albumin, expressed cytokeratin 18, transferrin, α1-antitrypsin, α-macroglobulin, GST (FIGS. I and Z), and very low levels of γ-GT. They were uniformly negative for α-fetoprotein and factor VIII. Therefore, THLE cells represent a population with a differentiation grade between oval cells and hepatocytes. The possibility that the THLE cells are derived from hepatocyte precursors such as oval cells cannot be ruled out. However, the fact that cytokeratin 18 is expressed and α-fetoprotein is absent in a very early stage of their establishment indicates a derivation from differentiated hepatocytes rather than oval cells. The appearance of cytokeratin 19 and the decrease in albumin secretion at later passages suggests that the cells dedifferentiate in culture, a process often seen as a consequence of transformation. In the in vitro model of normal liver epithelial cells described here, dedifferentiation is reversible because albumin expression can be induced in roller bottles and by growing cells on extracellular matrices or in tridimensional aggregates.**

Therefore, Harris does not disclose or suggest the essential features of the present immortalized hepatocytes, because the cells disclosed in Harris (1) are not derived from a normal

liver epithelial cell and (2) do not naturally produce endogenous therapeutic plasma proteins. Additionally, the cells disclosed in Harris are not stable in culture and undergo dedifferentiation.

Because Harris does not anticipate the present invention, the Examiner is respectfully requested to withdraw this rejection.

U.S. Patent No. 6,107,043 ("Jauregui")

The Examiner has rejected claims 1, 4-7, 9-22 and 30 under 35 U.S.C. § 102(b) as allegedly anticipated by Jauregui. This rejection is respectfully traversed.

Jauregui does not disclose or suggest immortalized hepatocytes that are able to avoid undergoing dedifferentiation. Jauregui discloses cells that undergo cell death in circumstances which lead to the expression of liver-specific proteins. At column 11, lines 37-41 of Jauregui it is stated:

> **For example, metabolic inducers, e.g., rifampin, phenobarbitol and methylcholanthrene, introduced into a low density culture of immortalized cells inhibited proliferation and actually increased cell death.**

These metabolic inducers should, in a differentiated liver cell, lead to the production of specific cytochrome P450 proteins to metabolize these foreign substances. This language also means that the cells of Jauregui fail to meet the requirement of the present invention that the immortalized hepatocytes "naturally produces endogenous therapeutic plasma proteins (TPPs)." In fact, there is no disclosure or suggestion in Jauregui that the cells naturally produce endogenous therapeutic plasma proteins.

Because Jauregui does not anticipate the present invention, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-7 and 9-32 under 35 U.S.C. § 103(a) as allegedly rendered obvious over Harris in view of U.S. Patent No. 6,653,105 ("Triglia"). This rejection is respectfully traversed.

The Examiner has the burden of presenting a *prima facie* case of obviousness. For an invention to be obvious under 35 U.S.C. § 103(a) requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. Indeed, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *See, KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), quoting *In re Kahn*, 441 F.3d 997, 988 (Fed. Cir. 2006)).

Here, Applicants respectfully maintain that the Examiner's articulated reasons for alleged obviousness do not have sufficient rational underpinnings to support a legal conclusion of obviousness. No *prima facie* case of obviousness has been established.

The combined disclosures of Harris, Jauregui and Triglia do not disclose or suggest any immortalized hepatocytes that are stable in culture and do not undergo dedifferentiation in culture, a required attribute of the claimed hepatocytes. This was discussed with respect to Harris and Jauregui above. Applicants also note that the cell line disclosed by Triglia produces reduced amounts of albumin with increasing passages in culture. *See*, Table 1 in column 16 of Triglia.

Moreover, simply identifying piecemeal the individual required characteristics of the claimed immortalized hepatocytes in different references does not direct the skilled person to produce an immortalized hepatocyte with all of the recited characteristics. If anything, Harris, Jauregui and Triglia are examples of failed attempts to produce an immortalized heptatocyte with the desired characteristics that Applicants actually achieved with the present invention. Also, in attempting to formulate the present obviousness rejection, Applicants respectfully submit that the Examiner has used impermissible hindsight reconstruction to assemble references that allegedly have the characteristics of the present immortalized hepatocytes. Nonetheless, even if it were possible to simply collect all of the attributes of the hepatocyte cell lines of Harris, Jauregui and Triglia into a single immortalized hepatocyte cell line, the hepatocyte cell line based on the combined disclosures of Harris, Jauregui and Triglia would undergo dedifferentiation in culture.

Accordingly, the combined immortalized hepatocyte cell line of Harris, Jauregui and Triglia falls short of the present invention even if cultured in serum free media.

In view of the foregoing, Applicants respectfully maintain that the present immortalized hepatocytes are nonobvious over the disclosures of Harris, Jauregui and Triglia. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Attachments
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